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Specification and Drawings, as originally filed, with Application for Patent Serial No: **2,411,569**, on November 12, 2002, by **ROSS E. MANTLE**, for "Medical Device for the Extravascular Recirculation of Fluid in Body Cavities at Controlled Temperature and Pressure".

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# MEDICAL DEVICE FOR THE EXTRAVASCULAR RECIRCULATION OF FLUID IN BODY CAVITIES AT CONTROLLED TEMPERATURE AND PRESSURE

## Abstract

A device for the prevention or treatment of a variety of disorders by means of automated local control of temperature and pressure in a body cavity. Appropriate body cavities are enclosed spaces containing organs in which biocompatible fluids excluding blood may be recirculated outside of blood vessels but inside the cavity (eg. subarachnoid space, peritoneum, mediastinum, pleural space). Fluid is pumped into the cavity by means of one pump and removed from it by means a second pump via a double-barreled catheter, with an optional secondary catheter for enhancement of the fluid distribution. A temperature and pressure sensor are mounted on the main catheter within the cavity. While outside the body, the fluid is ultraviolet-sterilized, foam fractionated to remove contaminants, oxygenated and pH balanced, cooled or warmed, and augmented with exogenous fluid that may contain drugs. Independent automated pump control allows adjustment of outflow based on cavity temperature and inflow based on cavity pressure. Pre-programmed temperature and pressure profiles can be executed over several days.

**Description**

## FIELD OF THE INVENTION

This invention relates to processes and devices for automated extracorporeal recirculation and chemical manipulation of biological and biocompatible fluids (eg. cerebrospinal fluid, artificial cerebrospinal fluid, saline, Ringer's lactate) in body cavities for the purposes of prevention or treatment of a variety of disorders. A process and device are disclosed for fluid recirculation via a single two-channel catheter inserted into a body cavity (eg. subarachnoid space, cerebral ventricular system, mediastinum, pleural space, peritoneum). Secondary drainage catheters may also be inserted as needed to enhance the distribution of the fluid. By means of automated feedback-controlled pumps and heating/cooling elements, the device allows control of the temperature and pressure of the fluid over short or long time periods (hours to days) according to predetermined protocols, and manipulations of the chemistry of the fluid. These manipulations may include dilution of with artificial fluids, removal of contaminants by foam fractionation, oxygenation, pH balancing, and addition of chemical agents or drugs.

## BACKGROUND OF THE INVENTION

A number of clinical situations exist in medicine in which automated control of the temperature, pressure and chemistry of fluid within a body cavity are likely to be therapeutically useful. These include:

1. Traumatic or ischemic brain and spinal cord injuries, in which temperatures below normal and control of pressure may improve outcome (reviewed below).
2. Hemorrhage in the regions of the brain and spinal cord, in which removal of blood may improve outcome (Deraco *et al.*, 2001).

3. Infection in the regions of the brain and spinal cord, in which addition of intrathecal antibiotics or antivirals (which bypass the blood-brain barrier) may be beneficial (Luer & Hatton, 1993). Hypothermia, hyperthermia, or oscillation between hypothermia and hyperthermia, pressure control, and removal of infectious organisms (pus) and inflammatory mediators from the cerebrospinal fluid (CSF) may also be beneficial.
4. Brain edema related to liver failure, in which hypothermia has been shown to be beneficial (Chatauret *et al.*, 2001).
5. Malignancy in the regions of the brain and spinal cord, in which hyperthermia has been shown to increase the efficacy of chemotherapy and radiation in the treatment of glioblastoma multiforme, the most common, and usually fatal, form of brain cancer (Sneed *et al.*, 1998).
6. Infection in the region of other body cavities, including peritonitis, pleuritis, and mediastinitis, in which the continuous delivery of antibiotic, antiviral, or related therapies under controlled temperature and pressure could be useful. Such therapies have been delivered into the peritoneum (Lye *et al.*, 1999) and other cavities (Sahn, 1998), but without feedback control of temperature or pressure.
7. Malignancy in the region of body cavities, including the peritoneum, pelvis, mediastinum, and pleural space, in which hyperthermia and/or the local delivery of chemotherapeutic agents have shown greater effectiveness than conventional therapies in some studies (Deraco *et al.*, 2001).
8. Ischemia of the intestine or colon, in which hypothermia might protect the tissues from ischemic damage (Vejchapipat *et al.*, 2002). Such protection may apply in other organs subject to ischemia, such as the heart.
9. During surgery involving any of the above regions, in which local hypothermia can decrease the metabolic demands of tissues, resulting in decreased susceptibility to injury and decreased bleeding due to lower blood flow. An automated device may also continue hypothermic therapy into the post-operative period, providing protection from post-operative adverse events such as stroke.

**Hypothermia in Brain and Spinal Cord Injuries**

Central nervous system (CNS) tissues, and particularly neurons, are among the most vulnerable in the body to a variety of injuries and disorders. Though investigations into the mechanisms of this extreme vulnerability have generated a wealth of interesting findings, these mechanisms are still unclear. As a result, many promising therapies for CNS injuries and disorders have been disappointing, and the mainstay of clinical treatment remains largely supportive. Temperature is a major determinant of the severity of traumatic and ischemic central nervous system (CNS) injuries. The protective effects of hypothermia applied during injuries has been extensively documented, and is currently in use intraoperatively in certain forms of brain surgery and cardiac surgery. The potential for hypothermic benefits is spinal cord injury may be similar to that in brain injuries, but published reports in this area are much less frequent. A recent report is available, however, which concluded that hypothermia was protective against ischemic spinal cord injury in the context of abdominal aortic aneurysm surgery in humans (Davison *et al.*, 1994). Given the significant potential for improvement in outcomes arising from the disclosed invention in the hypothermic treatment of traumatic and ischemic injuries of the brain, this area is reviewed in particular, with selected references.

**Hypothermia in Brain Trauma, Animals:** In an example of the use of hypothermia in the treatment of brain trauma, 2 h of immediate whole body hypothermia to 32°C was applied in rats subjected to an open controlled cortical impact injury. The rats were rewarmed slowly and subjected to beam balance function and Morris Water Maze memory acquisition testing over the subsequent fifteen days, followed by post-mortem histological assessments. The hypothermic groups had significantly preserved functional ability, although direct tissue damage (necrotic cavitation) assessed histologically was not significantly attenuated (Dixon *et al.*, 1998).

**Hypothermia in Ischemia, Animals:** Rats subjected to a global ischemia four-vessel occlusion model (4VO) and treated with intraischemic whole-body hypothermia to 30°C had preservation of maze learning at 2 mo post injury, and had minimal cell death in the CA1 hippocampal region, whereas untreated animals suffered substantial CA1 cell death and had impaired learning performance (Green *et al.*, 1992).

Whole body cooling to 33°C was used in a model of focal ischemia in which rats received 1 h of middle cerebral artery occlusion (MCAO) with monitoring of intracerebral blood flow. This study compared hypothermia, mannitol, and combined hypothermia and mannitol therapies. Hypothermia was more effective than mannitol in reducing neurologic deficit and infarct volume, and, unlike mannitol, did not result in an increase in cerebral blood flow. Combined therapy with hypothermia and mannitol was no better than hypothermia alone (Karibe *et al.*, 1995).

**Selective Brain Cooling (SBC) vs. Whole Body Cooling (WBC):** SBC appears to be as effective as WBC in some trials. Using a three-pronged outcome evaluation involving spatial memory (open field test) at 10 d post-injury, CA1 evoked potentials in brain slices at 3 weeks post-injury, and histological assessment, Nurse and Corbett found that intraischemic SBC to 31.4°C (with normal core body temperature) produced functional and histological results indistinguishable from controls after a 5 min forebrain ischemic insult in the 3-5 mo old gerbil. Normothermic ischemic animals had severe functional deficits, diminished field potentials and near total loss of dorsal CA1 cells (Nurse & Corbett, 1994). Park and colleagues directly compared SBC with WBC in a rat permanent MCAO model in which hypothermia was applied beginning 15 min post injury and continued for either 30 min or 1 h, then reversed by spontaneous rewarming. Cerebral blood flow was monitored by cortical laser dopper flowmetry and histological assessment was done at 24 h post injury. 30 min of either SBC or WBC showed no significant attenuation of infarct volume, while 1 h of cooling decreased infarct volume by 49.2% in WBC but only 26.6% in SBC. The authors concluded that WBC was more protective than SBC, but that the difference may have been due to rapid spontaneous rewarming in the SBC group. In support of this, a reactive hyperemia was observed by laser doppler flowmetry in the SBC group, but not the WBC group, during rewarming (Park *et al.*, 1998). It is expected that passive rewarming will proceed much more rapidly in SBC than WBC and thus may represent a particular hazard.

**Hyperthermia Worsens Brain Injury:** A corollary of hypothermic neuroprotection is hyperthermic neuroendangerment. This is borne out in both trauma and ischemia. A study by Minamisawa et al, for example, in which both intracerebral and rectal temperatures were controlled over a range of temperatures from 35-39°C, before,

during and shortly after a 2VO forebrain ischemic insult in the rat showed that hypothermia was protective and hyperthermia damaging according to histological assessments performed one week post-injury. The degree of protection or damage was symmetrical around a midpoint temperature of 37°C in certain brain areas, notably the neocortex. In general, hyperthermia produced effects similar to lengthening the duration of ischemia (Minamisawa *et al.*, 1990).

Spontaneous body and brain hyperthermia after ischemia is a very common response to injury which may contribute significantly to the degree of damage. The mechanism of this effect may be hypothalamic dysregulation, brain hypermetabolism, or a decreased circulatory capacity to remove brain heat (Harris *et al.*, 2002;Schwab *et al.*, 1998). Interestingly, hyperthermia can significantly worsen outcome even it is delayed by many hours. In a study by Kim et al, rats subjected to 1 h MCAO were allowed to recover in a normal environment for 24 h, then placed under awake brain temperature feedback control at a range of temperatures from 37-40°C for 3 h. Behavioural and histological assessments three days later showed that the 40°C group had significantly larger infarct volumes and poorer functional scores (Kim *et al.*, 1996). Similar results have been obtained using a fluid percussion brain trauma in rats. Hyperthermia with cerebral temperature monitoring applied 24 h after the insult resulted in a significant 47% higher mortality, larger contusion volume and greater microstructural damage than in normothermic controls (Dietrich *et al.*, 1996).

These findings have major clinical implications. Hyperthermic brain temperature was found to be a strong predictor of elevated intracranial pressure in a study of 20 head trauma patients (Rossi *et al.*, 2001). An observational study of 390 acute stroke patients found that body temperature on admission was an independent predictor of stroke size, mortality and functional outcome (Reith *et al.*, 1996).

**Delayed Hypothermia:** Since most acute brain injuries occur outside of hospital, the delay prior to treatment is almost always greater than 30 min. Disappointing early results with delayed hypothermia, and the resultant widespread notion of a narrow 'therapeutic window' dampened enthusiasm in this area for many years. Colbourne and colleagues reviewed a collection of early reports in which both immediate and delayed hypothermia were ineffective or harmful in ischemia. They were able attribute negative results in most cases to 1) insufficient duration of hypothermia in relation to injury severity, 2) uncontrolled or rapid rewarming, and 3) the harmful

effects of deep whole-body hypothermia (<30°C) on the hematologic and cardiorespiratory systems (Colbourne *et al.*, 1997).

Recent reports suggest that much longer hypothermic times than were previously contemplated can compensate for delays in treatment and produce outcomes comparable to intra-injury or immediate hypothermia. In their widely quoted 1995 study using a negative feedback-controlled automated whole body temperature controller for awake rodents (Colbourne *et al.*, 1996). Colbourne and Corbett showed that CA1 cell preservation and attenuation of behavioural deficits persisted for six months in gerbils subjected to a 5 min forebrain ischemic insult with 24 h of 32°C WBC begun 1 h after the insult. 70% CA1 preservation was observed at six months. This represents a decline from 90% at 30 d, but remained statistically significant. More importantly, the preservation of neurologic function appeared undiminished. Lesser, but statistically significant, treatment effects were also observed at a temperature of 34°C, or when the treatment was delayed by 4 h (Colbourne & Corbett, 1995). These authors also report continued, ostensibly permanent, protection at 1 y post injury in three gerbils who underwent the original protocol, and significant protection after a treatment delay of 12 h with a longer treatment protocol of 24 h at 32°C followed by 24 h at 34°C (Colbourne *et al.*, 1997). A study of 2VO forebrain ischemia in fetal lambs by Gunn and colleagues involving both delayed hypothermia and SBC deserves mention. In this study, near term fetal lambs were surgically instrumented *in utero* with inflatable occlusion cuffs around both carotids and a cooling coil was wrapped around the fetal cranium. The coil was activated 90 min after a 30 min period of forebrain ischemia, maintaining an extradural temperature of 27-32°C for 72 h. Lambs under this form of SBC had much greater return of EEG activity and a 60% reduction in cortical neuronal loss at five days (Gunn *et al.*, 1997).

In focal ischemia, Kollmar and colleagues have reported a 2 h MCAO model in which 5 h of 33°C WBC was applied 1 h post-injury. Rats were followed by serial MRI and Menzies neurological function scores for five days, at which point the brains were examined histologically. This comparatively brief treatment improved survival, functional scores, edema volume and infarction volumes (Kollmar *et al.*, 2002).

With regard to trauma, WBC to 30°C for 3 h after a treatment delay of 1 h reduced edema and improved neurological scores over a 5 d evaluation period in rats subjected to a controlled cortical impact injury. These benefits were not observed if

the delay was increased to 1.5 h or 2 h. Edema was noted to reach a peak at 24 h and remain elevated in normothermic animals, but not treated animals (Markgraf *et al.*, 2001). Again, the hypothermic duration used here was relatively brief, perhaps for lack of availability of an automated controller.

**Hypothermia in Humans:** Accounts of remarkable recoveries in humans submerged in cold water for >20 min have been documented, and the use of deep intra-operative hypothermia (<27°C) as a neuroprotective maneuvre in cardiac bypass surgery and in brain surgery requiring the interruption of circulation has been established for many years (Maher & Hachinski, 1993). The utility of whole body hypothermia in human stroke and human head injury, however, is less clear.

In a study of severe head injury, Glasgow Coma Scale (GCS) ≤ 8, Jian et al randomized 87 patients to 33-35°C using cooling blankets and muscle relaxants or normothermic maintenance (37-38°C). Target temperature was reached in a mean of 15 h post-injury and gradual rewarming was commenced when intracranial pressure (ICP) returned to normal, resulting in hypothermic durations of between 3 and 14 d. One year later, mortality was 26% in the hypothermic group with Glasgow Outcome Scores (GOS) of 4-5 (good to moderate disability) in 47%. In the normothermic group, mortality was 45% and GOS 4-5 was found in only 27%. Hypothermia markedly reduced intracranial pressure and hyperglycemia without significant side effects (Jiang *et al.*, 2000). A randomized trial of 82 patients with GCS 3-7 was undertaken by Marion and colleagues, in which WBC to 33°C was achieved in a mean of 10 h post-injury. 32-33°C hypothermia was maintained for 24 h and evaluations were done over the subsequent year. The hypothermic group enjoyed 62% good outcomes, while the normothermic group had only 38%. The treatment was beneficial in patients with GCS 5-7, and ineffective in those with lower GCS. In a subgroup analysis of GCS 5-7 patients, statistically significant benefits were observed at 3 and 6 months post injury, but not at 12 mo. (Marion *et al.*, 1997) A larger study of 392 patients concluded that there was no significant outcome difference at six months between comatose head injury patients treated with 33°C WBC initiated within 6 h and maintained for 48 h. The patients in the hypothermic group had lower ICP's, but longer hospital stays due to non-neurological complications (Clifton *et al.*, 2001). A 2002 meta-analysis of 12 trials of 34-35°C WBC for at least 12 h from the Cochrane Database came to a similar conclusion, namely that the neuroprotective

benefits of hypothermia may have been overcome by high rates of pneumonia and other side effects (Gadkary *et al.*, 2002). Another 2002 meta-analysis of 7 studies with a broader set of inclusion criteria also concluded that there was no benefit from hypothermia. The meta-analysis showed that although ICP was again found to be greatly decreased, hypothermia was again associated with substantial increases in the rates of pneumonia, cardiac arrhythmia, and prothrombin and partial thromboplastin time abnormalities (Harris *et al.*, 2002).

The few clinical studies of hypothermia in stroke tell a similar story. A landmark uncontrolled pilot study by Schwab and colleagues conducted in 1998 subjected 25 intubated patients with severe, space-occupying MCA stroke to 33°C WBC for 48-72 h after a mean delay of 14 h. 56% of patients survived with a mean Scandinavian Stroke Scale score of 38 (neurologically intact score = 60) at 3 mo. This was compared *ad hoc* with the expected 80% mortality from space-occupying stroke. The remaining patients all died from brain herniation due to acute elevations of ICP on rewarming. Study patients also suffered a widely quoted 40% incidence of pneumonia (Schwab *et al.*, 1998). A Cochrane Database review from the year 2000 commented that there were no randomized or controlled trials in this area, and hence no evidence for the routine use of hypothermia in stroke (Correia *et al.*, 2000).

It seems likely that the systemic complications of prolonged whole-body hypothermia are a major barrier to the effectiveness of this therapy in either stroke or trauma. Hence, hypothermia is a therapy in search of a safe delivery method.

**Selective Brain Cooling (SBC) in Humans:** It is possible that the SBC approach could be as effective as WBC without the production of systemic complications. As a result, some investigators have focused on a human SBC strategy. Unfortunately, SBC is very difficult to achieve in large animals such as humans. Compared with smaller animals, the human head has a low surface area-to-volume ratio and a high degree of thermal inertia. The human brain is insulated from the surface of the head by approximately 2.5 cm of highly vascular scalp, bone, meninges and cerebrospinal fluid (CSF). In addition, the brain receives constant thermal input in the form of 20% of the cardiac output, or 1 L/min of blood at 37°C. Zhu and Diao developed a computer model of the thermal properties of the human head, and concluded that the maximum volumetric mean temperature gradient obtainable between the brain and the body of an adult was 1.7°C under maximal cooling of the head surface (Zhu & Diao,

2001). A real-world experiment has been carried out in which the surface temperature of the human head was reduced to 15°C for 50 min and the brain temperature measured using an MRI technique. No change in brain temperature was detected (Corbett & Laptook, 1998).

An alternative to surface cooling is intra-arterial cooling using either bypass-cooled blood or intra-arterial cooling probes. Schwartz and colleagues maintained bilateral brain temperatures of <25°C for three hours in anaesthetized baboons. Blood was withdrawn from the femoral artery, cooled and reintroduced via an occlusive cannula in one carotid (Schwartz *et al.*, 1996). With regard to intra-arterial cooling probes, numerous patents in the USPTO database relate to such methods. Such an approach requires very low temperatures at the probe tip due to the high flow velocities of carotid blood. Both intra-arterial approaches suffer from the major inherent risk of endovascular instrumentation of the cranial arteries in general; that of precipitating stroke. To minimize this risk, such instrumentation is normally done under full dose heparin anticoagulation. This presents a problem, since the risk of intracranial bleeding may contraindicate heparinization in both trauma with hemorrhage, and severe stroke.

**Cerebrospinal Fluid (CSF) Cooling:** The use of CSF as a coolant may have a precedent in normal physiology. Based on anatomical considerations, it has been suggested that the normal brain temperature of approximately 1°C below body temperature is due to cooling interactions between CSF and scalp veins (Cabanac, 1993;Zenker & Kubik, 1996). No methods for cooling the CNS via the CSF are to be found in the medical literature or in routine clinical use. However, there are two US patents that relate to devices which use CSF as a means of applying hypothermia.

US Patent no. 4,904,237 (Janese, 1990) discloses a CSF exchange system which removes CSF from the lumbar cistern, filters out blood contaminants, cools, pH adjusts and performs diagnostic measurements, then returns the CSF to the lumbar cistern by reversal of flow in a reciprocating pump arrangement. This system seems intended primarily for the removal of subarachnoid blood from the CSF in the context of subarachnoid hemorrhage. In the preferred embodiment, 10 ml of CSF are exchanged in 25 s cycles, giving a flow rate of 24 ml/min. If the temperature of the returned CSF is at 4°C, this flow rate may not be adequate to achieve significant cooling in the spinal cord, where published flows of approximately 30 ml/min were

required in a human trial (Davison *et al.*, 1994). Another problem with this design is that the catheter may be prone to blockage during the suction phase of the cycle by blood products, nerves or other soft tissues.

US patent no. 6,379,331 (Barbut, 2002) discloses another medical device for intrathecal cooling of the spinal cord in which separate inflow and outflow catheters are inserted into the CSF spaces of the spinal cord such that their tips are at either end of the region to be cooled. CSF is extracted from one catheter, cooled, and returned to the second catheter by means of a single pump without automated feedback control. The flow rate of the single pump is adjusted to keep intraspinal pressure (as estimated from the pressure of the extracorporeal fluid, and not from measurement within the cavity) below a safe level. This system is intended primarily for intraoperative spinal cord cooling in the context of abdominal aortic aneurysm surgery, which carries a high (~10%) risk of paraplegia related to spinal cord ischemia during cross-clamping of the aorta. Alternate placement of one of the catheters into the lateral ventricle of the brain is disclosed as a method of cooling the brain, although practical brain cooling would seem unlikely due to flow rate limitations. A difficulty with any catheter arrangement in which the catheter tips are separated in space is that pressure differentials proportional to the separation distance occur between the inflow and outflow regions at higher flow rates. Hence, the maximal flow is limited by the maximal safe pressure in the region of the inflow catheter, where pressure is high. Placement of two catheters in the brain ventricular system such that their tips are relatively close together is a potential means of diminishing this problem for brain cooling; but this approach suffers from the disadvantage of having to pierce the brain twice, doubling the risk of intraparenchymal hemorrhage (10%) due to catheter placement (Wiesmann & Mayer, 2001).

US patent no. 4,445,500 (Osterholm, 1984) discloses a treatment for stroke involving the recirculation of an oxygenated perfluorocarbon emulsion through a portion of the subarachnoid (CSF) space. This system is intended to counteract a variety of central nervous system injuries in which a component of the injury is ischemia by providing sufficient oxygen in the perfusate to allow continued neural tissue metabolism in the presence of insufficient blood flow. The system depends on an involved process for the manufacture and maintenance of the perfluorocarbon emulsion. The biocompatibility of such an emulsion is more doubtful than, for example, saline-based solutions. As in the previously discussed patent, a single pump

is again used for circulation of the fluid within the subarachnoid space, which precludes active pressure modulation, and the inflow and outflow catheters are again separated. The low flow rates possible under this configuration (<60 ml/min) are disclosed as sufficient for adequate brain oxygenation with the emulsion used. Intracranial pressure measurements are made by means of a double lumen catheter, one lumen of which is devoted to pressure measurements (not fluid flow). The infusion rate into the brain is adjusted manually to keep the pressure below a safe limit. The temperature of the emulsion may be adjusted extracorporeally, but no measurements of temperature are made within the CNS. Together with the low flow rates, this would seem to preclude practical and precise therapeutic temperature modulation. Precise control of temperature is required in hypothermic CNS therapy, particularly during the dangerous rewarming stage, and to an even greater extent in therapeutic hyperthermia for many different organs, in which overheating can severely damage normal tissue. The system calls for microfiltration of the emulsion as a means of removing bacteria, but discloses no means of removal of other contaminants, such dissolved proteins or blood products.

**Fluid in non-CNS body cavities:** With regard to the continuous recirculation of fluids in other body cavities, several US patents disclose devices for recirculation of fluids in the peritoneal cavity (eg. US patent no. 6254567, 6409699, and 5141493). These examples are dialysate circulators for the purpose of continuous flow-through intraperitoneal dialysis (CFPD) for the treatment of kidney or liver failure. Many of these designs incorporate a heater whose purpose is to warm the dialysate to body temperature before it enters the body, but therapeutic temperature modulation is not encompassed. They generally feature a means of maintaining constant pressure of the dialysate fluid extracorporeally, but do not accomplish pressure modulation within the cavity by use of independent inflow and outflow pumps. These devices are also not intended for the delivery of drugs or the removal of contaminants such as blood or pus.

With regard to other cavities, including the pleural space and mediastinum, no device similar to the present invention appears to have been disclosed either in the medical literature or the awarded US patent database.

**Foam Fractionation:** Foam fractionation is a technique for the removal of proteins and other contaminants from saline or other suitable fluids. This technique is often used in marine aquaculture, where it is commonly known as 'protein skimming'. Dissolved amphipathic (partly water soluble and partly non-water soluble) molecules such as proteins tend to accumulate at an air/water interface since part of the molecule is more stable when dissolved in aqueous solution and part is more stable in air. Such molecules can be removed with high efficiency from liquids of suitable composition by saturation of the solution with fine bubbles. The bubbles accumulate proteins at the air/water interface and the resulting foam rises to the top of the liquid, where it may be collected or skimmed off. As an additional benefit, the intimate contact of air or of a gas mixture containing oxygen can oxygenate the fluid. Contact of an oxygen-carbon dioxide gas mixture with a bicarbonate-buffered solution, for example, can both oxygenate and pH balance the solution. US patents no. 6436295, 5562821, 5554280, 5122267, 5665227, and 5380160, for example, describe devices for foam fractionation in marine aquariums. Foam fractionation is also used in the purification of proteins and drugs in the pharmaceutical industry. No references in the medical literature or the awarded US patents database are found which relate to the use of foam fractionation in the purification of a bulk fluid for recirculation within a body cavity.

## SUMMARY OF THE INVENTION

A system of automated selective regional temperature, pressure and fluid composition control via cooling or heating, foam fractionation, and recirculation of a biological or biocompatible fluid in a body cavity is disclosed.

**Device description:** A single double-barreled catheter is inserted into the body cavity, of which one barrel is for continuous outflow from the cavity and the other for continuous inflow to the cavity. The catheter incorporates a sensor located along its length (but thermally insulated from it) which is capable of sensing both the temperature and pressure of the interior of the cavity in the vicinity of the catheter shaft. Fluid is continuously withdrawn by means of an outflow pump via sterile tubing. The resulting flow is monitored by means of a flow sensor. The fluid is

discharged into a conditioning chamber irradiated by short wave ultraviolet light capable of sterilization of the fluid. The fluid in the conditioning chamber is continuously permeated by fine bubbles of gas from a pressurized gas source. Artificial biocompatible fluid is continuously added to the chamber by gravity feed from an external reservoir (eg. hanging bag), and the excess fluid is drained into a waste reservoir from an overflow aperture in the chamber. This overflow also collects surface foam containing concentrated contaminants extracted by the foam fractionation effect of the bubbles. At the same time, the liquid in the conditioning chamber is cooled by means of refrigeration of the chamber walls or warmed by means of heating of the chamber walls. The temperature is feedback-controlled by means of a temperature sensor in contact with a portion of the chamber. Fluid is then withdrawn from the chamber by means of a second pump and the resultant flow is again monitored. Finally, the fluid is discharged into the body cavity via the inflow barrel of the double-barreled catheter. A second catheter which drains fluid at a slower rate relative to the main catheter by means of a similar pump and flow sensor arrangement may be positioned in a distant portion of the body cavity to improve distribution of the recirculated fluid. Throughout this process, the flow rates of the inflow and outflow pumps are feedback-regulated based on intra-cavity temperature and pressure information relayed from the sensor in the main catheter. Flow in the secondary catheter is regulated based on information from a sensor capable of measuring the temperature of the fluid removed by this catheter. By appropriate regulation of the inflow and outflow rates, desired temperature and pressures are achieved within the cavity (further explanation below). Preprogrammed temperature and pressure profiles can be executed over several days by means of a system of computer programmed automated microcontrollers. At the same time, drugs or other agents may be added to the circulating fluid via the external reservoir. Gaseous exchange with the bubbled gas can, depending on the composition of the gas, oxygenate and adjust pH while contaminants removed by foam fractionation are removed and collected as waste.

**Catheters:** Co-location of the inflow and outflow barrels as elements of the same catheter implies that a portion of the inflow will be immediately drawn into the outflow. However, a considerable dispersion rate, estimated to be 50%, of fluid away from the catheter will occur, and the flow rate can be increased over a broad range

without creating harmful pressure differentials. An alternate embodiment in which the inflow and outflow barrels are not part of the same catheter but are located in close proximity to one another is also disclosed. A secondary outflow catheter with its own outflow pump may be located in a distal portion of the cavity to improve the distribution of the circulated fluid. As an example, spinal cord cooling might be accomplished by means of a double barreled catheter in the cervical subarachnoid space, with a secondary drainage catheter in the lumbar cistern. The body of cooled fluid in the cervical region would then be drawn toward the secondary drainage catheter such that effective cooling could be extended throughout the spinal cord. A temperature sensor capable of detecting the temperature of the fluid removed by means of this catheter is used in a feedback arrangement to control the flow rate in the secondary catheter. If the temperature is higher than the intra-cavity target temperature in a hypothermic protocol, for example, this indicates that the cooled fluid is not sufficiently distributed in the region of the secondary catheter. The secondary outflow rate is then increased until an adequate distribution is achieved.

**Control of Temperature and Pressure:** The temperature within the cavity is a function of the overall flow rate (given constant perfusion within the cavity by the blood circulation). The greater the overall flow, the more closely will the intra-cavity temperature approach that of the fluid in the conditioning chamber. In practice, overall flow rate can be set by fixing either the inflow rate or the outflow rate at a constant value. Intra-cavity pressure, on the other hand, is a function of net fluid removed or added to the cavity. The system can actively regulate pressure by transiently removing more fluid than it replaces, or vice versa. When inflow exceeds outflow, the pressure will rise. Conversely, when the inflow rate is less than the outflow, pressure will fall. Hence, the inflow rate may be transiently varied to produce a broad range of desired pressure within the cavity in the presence of approximately constant overall flow. In the context of open surgery, in which the cavity is at least partially open to atmospheric pressure, for example, flow adequate to maintain the desired temperature while adding no extra pressure (inflow = outflow) can be achieved.

**Compliance monitoring:** The disclosed invention allows for the automated measurement of compliance within a cavity. Compliance is the change in pressure per

unit change in the volume of a cavity's contents (or vice versa), often expressed in ml/mmHg. The disclosed invention can monitor compliance by periodically stopping both inflow and outflow, then delivering a known volume of fluid into the ventricle and recording the pressure response. In the intracranium, for example, normal compliance values are within the range 0.5-1.4 ml/mmHg. A critically low compliance of <0.5 ml/mmHg is thought to reflect a dangerously volume-overloaded intracranium which is likely to be underperfused (Portella *et al.*, 2002). Both high intracranial pressure and low compliance predict adverse outcome, but critical compliance changes tend to precede critical intracranial pressure changes (Kiening *et al.*, 2002). Also, the disclosed invention precludes monitoring unperturbed pressure, since this parameter is under active control, therefore compliance monitoring may be particularly helpful, especially in the context of the need to slow the rewarming process if the brain exhibits low compliance.

**Automation:** Automated control of the system is achieved by means of a series of sensor inputs and control outputs to the system hardware from a computer-based device running a program of feedback loops. In one embodiment, the computer-based device is a microcomputer which can download a series of programmed instructions to an embedded microcontroller, which communicates with the hardware via serial port and a digital-to-analog/analog-to-digital (DAC/ADC) conversion units. In this embodiment, the purpose of the embedded microcontroller is to allow continued operation of the feedback loops in the event of a malfunction of the microcomputer. In another embodiment, failsafe functionality is achieved by the use of at least two computer-based control systems operating in parallel such the failure of one system can be compensated by the other. The invention also incorporates an uninterruptible power supply using battery back-up for the temporary continued operation of all electrically operated components in the event of disconnection or failure of the mains supply. A further safety feature is the use of an electrical circuit running within the tubing and connectors which is closed while the main input and output tubing is connected to the main catheter, but becomes open in the event of disconnection of the tubing from the main catheter. Inputs to the computer-based control system include: intra-cavity temperature and pressure, inflow and outflow rate from the primary catheter, outflow rate from the secondary catheter, temperature of the fluid in the conditioning chamber, temperature of the fluid emerging from the secondary catheter,

connection status of tubing to main catheter, and status of battery power supply. Outputs from the computer-based control system include: on/off, rate and pumping direction of the inflow and outflow pumps for the primary catheter, on/off, rate and pumping direction of the outflow pump for the secondary catheter, and heat/cool and power level of the heating/cooling elements. Sensor data and program status are continuously displayed by the computer-based system during operation.

**Feedback Loops:** Several concurrent PID (proportion integration derivative) tuned feedback loops are used to bring the controlled variables to pre-programmed values.

1. Outflow vs. Temp: Outflow from the main catheter is adjusted based on the intra-cavity temperature such that flow is increased until the temperature reaches the desired value, and decreased if temperature exceeds the desired value (either too low in the case of hypothermic temperatures or too high in the case of hyperthermic temperatures).

2. Inflow vs. Pressure: Inflow from the main catheter is increased if the intra-cavity pressure is below the desired value and decreased if it is above the desired value.

3. Outflow of the secondary catheter vs. temperature of fluid in the secondary catheter: Outflow from the optional secondary catheter, which is low compared with outflow from the main catheter, is adjusted based on the temperature of the fluid as measured at some point within the outflow pathway. The flow rate is increased until the temperature comes to within a preset range of the temperature at the main catheter to ensure adequate distribution of fluid within the cavity.

4. Pump Rate vs. Flow: The pump rates (RPMs) are feedback adjusted based on flow to achieve the desired flow values.

5. Compliance/Clearing routine: In a situation in which compliance parameters are monitored as an indication of intra-cavity perfusion, such as in brain cooling, the compliance is monitored at intervals (eg. every 2 min.) as described above. This monitoring may be particularly useful during the rewarming phase after brain hypothermia, in which reactive hyperemia of the brain can result in a dangerous drop in compliance, i.e. monitoring of compliance allows slowing or reversing of rewarming until compliance values normalize. The compliance monitoring routine has the additional function of periodically clearing the outflow catheter to prevent blockage, and is initiated if a blockage is detected by means of a drop in flow relative to pump rate in either the main catheter or the secondary catheter.

**Magnetic Resonance Imaging (MRI) Compatibility:** Medical MRI is a technique of diagnostic imaging in which the spatial location, and some of the kinetic and chemical properties of a number of paramagnetic atoms within a patient's body can be determined and displayed as an image. The patient's body is placed within a strong magnetic field (>1 Tesla) and radiofrequency pulses of electromagnetic energy (EM) are delivered to the body which disturb the orientation of the paramagnetic atoms. Information used to form the image is then derived from measurements of EM re-radiation arising from the reorientation of these atoms in the field. Medical devices compatible with this form of imaging must be nominally free of bulk paramagnetic materials and shielded against emission or exposure to radiofrequency EM. An embodiment of the present invention is disclosed in which pumps made of non-paramagnetic materials are operated by compressed air, hydraulic, or other non-magnetic form of propulsion, the means of heating and cooling consist forms of refrigeration/heating which do not rely on electric motors in close proximity to the patient (eg. Peltier elements), no bulk paramagnetic materials are used, and the electronics are adequately shielded.

## BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 Block diagram of an embodiment of the invention depicting the main components and their interconnections. The main (1°) catheter 8 is inserted into a body cavity while the optional secondary (2°) catheter 1 is inserted into a distal portion of the cavity to improve distribution of the recirculated fluid.

Fig. 2A Detail of the preferred embodiment of catheter tip for main catheter (cut from the catheter shaft). The left barrel 18 removes fluid from the cavity while the right 21 infuses fluid into the cavity.

Fig. 2B Depiction of flow patterns surrounding a cross-section of the catheter tip.

Fig. 2C Depiction of main catheter with longitudinally-mounted intra-cavity temperature/pressure sensor 23.

Fig. 3 Detail of the preferred embodiment of the conditioning chamber.

Fig. 4A Depiction of anatomical sites in which the main catheter can be positioned. Positioning in the lateral ventricle of the brain 31, the peritoneal cavity 32, and the pleural space 33 are depicted.

Fig. 4B Example of positioning of the primary catheter 34 in the C1-C2 subarachnoid space and the secondary 35 in the lumbar cistern for spinal cord cooling.

Fig. 4C Example of positioning of the primary catheter 36 in the lateral ventricle of the brain and the secondary catheter 37 in the C1-C2 subarachnoid space for brainstem cooling.

Fig. 5 Brain temperature and pressure data collected from a proof-of-concept study in an anesthetized pig.

## DETAILED DESCRIPTIONS AND PREFERRED EMBODIMENTS

Fig. 1 Block diagram of an embodiment of the invention depicting the main components and their interconnections. To the left of the diagram, the optional single-barreled secondary catheter 1, which is inserted into a distal portion of the cavity if required to improve distribution of the recirculated fluid, is connected via sterile tubing to a pump 2. A sensor capable of measuring the temperature of the fluid withdrawn from catheter 1 is located at some point in the fluid pathway (not shown), preferably near the catheter itself. In the preferred embodiment, the pump is a peristaltic, single channel pump capable of >150 RPMs powered by an electric motor, or, in the case of the MRI compatible embodiment, by compressed air, hydraulic or other means. Sterile class VI tubing of ¼" internal diameter is preferred. One skilled in the art will appreciate that there are a large variety of pump and tubing types available which can also serve the purpose and fall within the scope of the invention. Some of the pumping functions described herein, such as that of the secondary outflow pump 2 may also be accomplished by gravity flow adjusted based on the

difference in elevation between the catheter and the point of discharge, although this would limit the range of available flow rates and is not preferred. The fluid then flows through a flow sensor 3, which, in the preferred embodiment, is an ultrasonic transit time sensor that clamps onto the outside of the tubing. Again, a variety of flow sensing technologies are available which could also serve this purpose and fall within the scope of the invention. The fluid is then discharged into the conditioning chamber 7. Flow from the outflow barrel of the main catheter 8 is similarly pumped through pump 5 to flow sensor 6 and enters the conditioning chamber 7.

In the conditioning chamber 7, the returned fluid undergoes sterilization by means of an ultraviolet (UV) lamp 4, foam fractionation by fine gas bubbles, and oxygenation and pH balancing or other chemical transformations depending on the gas and the fluid used. The overflow of concentrated contaminants is collected in a waste receptacle 10.

Fluid leaving the chamber passes through flow sensor 17 to pump 16 and is discharged through the inflow barrel of the catheter into the body cavity. Continuous alimentation of the system with fresh fluid from an elevated receptacle 9 (an IV-type bag is preferred) is accomplished via passage of fresh fluid through a drip chamber 11 to a junction 13 connected to the outflow tubing. The preferred rate of alimentation for a central nervous system application is 100-150 ml/h. For larger cavities with greater fluid absorption, such as the peritoneum, a faster rate may be required. The addition of external fluid to the system provides a means of ensuring adequate fluid levels in the chamber 7, adding drugs, modulating the composition of the recirculated fluid, diluting contaminants, and driving the overflow of contaminant-laden foam toward the waste receptacle 10.

Pressure and temperature are continuously monitored by means of sensors mounted on the main catheter. In the preferred embodiment, this is a strain gauge sensor referenced against the atmosphere to measure intracavity pressure and a temperature sensor using thermocouple or RTD technology. Other sensor technologies are available for the measurement of pressure and temperature, including the use of fiberoptic interferometry, and are intended to fall within the scope of the invention. The metering unit 12 is connected with the sensors on the main catheter.

In the preferred embodiment, the chiller/heater unit 14 is a solid state device which makes use of Peltier elements to cool or heat the walls of the chamber 7 directly. Such devices are now capable of cooling at the rate of five hundred to several

thousand Watts. More conventional recirculating chiller/heaters are also available which would serve this purpose well and fall within the scope of the invention. The gas is stored in a compressed gas cylinder 15 with regulator. This is connected with one or more airstones in the chamber, preferably sterilized limewood blocks, which discharge a fog of fine bubbles into the fluid.

All sensor data and control outputs are routed through the computer automated control system. These inputs are outputs are indicated on the diagram.

Fig. 2 Preferred embodiment of the main catheter. In fig. 2A, the left barrel 18 removes fluid from the cavity through orifice 19, while the right barrel 21 infuses fluid into the cavity through orifice 20. The internal diameters of these barrels are on the order of 2 mm for placement in the central nervous system, but larger for use in other body cavities. Both barrels are tipped with rounded caps 22, which will help the catheter pass through tissue smoothly on insertion. Note that the apertures of both barrels may be blocked by stiffening guide wires during insertion, both to aid in placing the catheter in the desired location and to prevent fouling of the apertures with tissue during insertion. Other catheter geometries with two lumens for conducting inflow and outflow, including coaxial lumens, and variations of the tip apertures are also intended to fall within the scope of the invention.

Fig. 2B shows the flow patterns at the outflow (left) and inflow (right) of a cross-sectional view of the preferred embodiment of the catheter tip. As depicted, jets of fluid emerging from the inflow barrel pass partially across the aperture of the outflow. Hence, particulates or soft tissue within the cavity are deflected from the outflow aperture to prevent outflow blockage.

Fig. 2C A depiction of the main catheter with pressure and temperature sensors 23 mounted in the groove between the barrels and thermally insulated from the barrel by a layer of non-thermally conductive material. The pressure/temperature sensors in the preferred embodiment are approximately 1.0 mm in diameter and may be mounted together as one unit (as shown) or separately in the grooves on opposite sides of the catheter.

Fig. 3 Detail of the preferred embodiment of the conditioning chamber. It is preferred, though not required, that the chamber be constructed of transparent or translucent plastic with good thermal conductivity, since the chamber and tubing are intended to

be disposable. The preferred shape of the chamber as a whole, as depicted, is a rectangular prism. This shape can have a larger surface area-to-volume than a cylinder of the same height and volume and has the advantage of presenting two large flat surfaces to the heater/chiller plates (not shown for clarity) which are in contact with the large anterior and posterior walls. This shape also maximizes the transit time of the fluid through the bubble path, which increases the efficiency of foam fractionation. It will be noted, however, that a variety of different chamber shapes and configurations may also serve this purpose and are intended within the scope of the invention. For central nervous system therapy, the dimensions of the chamber are such that the volume of the main reservoir 28 is 1 L. For cavities with larger fluid capacity, such as the peritoneum or pleural space, this volume is on the order of 3 L or more.

Flow returning from the outflow(s) enters the small reservoir 24, which provides a reserve of fluid for performing compliance measurements (which involve a temporary reversal of the outflow). The small reservoir 24 overflows onto a plate constructed of UV-transparent material. The exposure of the fluid to UV as it passes over this plate is intended to completely sterilize the fluid and may enhance foam fractionation (by partial denaturation of dissolved proteins), while the UV transparency of the plate is intended to allow irradiation of the main reservoir as a further safeguard. Apertures 26 in the distal end of the plate allow the fluid to drip into the main reservoir 28. One or more airstones 30 discharge a fog of fine gas bubbles into this reservoir, which concentrate contaminants at the surface by foam fractionation. Since the recirculating fluid is continuously augmented, a continuous overflow of the main reservoir 28 into the waste collection reservoir 27, allows collection of the contaminants. Alternate embodiments of the foam fractionation process encompass removal of the surface foam and fluid by active suction, or by collecting the foam in a cup as it rises in the confined space above the fluid (which would require an alternate chamber geometry). Gas-fluid contact may be alternately achieved by violently mixing the fluid and gas by means of a motor-driven impeller, introduction of gas into a fast-moving stream of fluid using a pump-driven Venturi tube, spraying a jet of gas and fluid into the reservoir, or passing the fluid at high velocity through a series of obstacles in a container suffused with the desired gas (downdraft skimmer).

Fluid intended to re-enter the body is withdrawn from a port at the lower extremity of the main reservoir in region 29. A mesh filter at the mouth of this port (not shown) prevents entry of stray bubbles into the inflow stream. In the preferred embodiment, a temperature sensor is located under area 29 of the chamber, in contact with the chamber floor. Temperature information from this sensor is used to regulate the heater/chiller to achieve the desired fluid temperature.

Fig. 4 Anatomical diagrams of human head and torso in lateral transparent view with multiple catheter placements. The main catheter is depicted in 4A in the peritoneum 32, the pleural space 33, and in the ventricular system (lateral ventricle preferred) of the brain 31. These are three important cavities in which continuous recirculation of fluid at controlled temperatures and pressures with removal of contaminants and/or addition of drugs could have important benefits. Catheter access (usually for the placement of passive drainage catheters) to each of these sites is routine for those skilled in the appropriate areas of medicine. Another cavity amenable to catheterization for this purpose is the mediastinum. Other cavities are also possible sites for catheterization. The cisterna magna of the brainstem, for example, would allow access to the intracranial subarachnoid space without piercing the brain parenchyma. Currently, however, access to this area is not routine.

In 4B, a catheter arrangement suitable for spinal cord injury, for example, is depicted. The main catheter 34 is depicted in the subarachnoid space at C1-C2 (cervical vertebrae one and two, not shown) while the secondary drainage catheter 35 is located in the lumbar cistern. Since the subarachnoid space contains CSF fluid in continuity over the length of the spinal cord, this arrangement will promote more even temperature modulation over the length of the spinal cord than would be possible with a single catheter. The main catheter position takes advantage of the generous size of the subarachnoid space at C1-C2 (approximately 1.5 cm anteroposteriorly). Catheterization of the C1-C2 subarachnoid space is routinely done by neuroradiologists under fluoroscopy. Lumbar puncture at the L2-S1 levels is routinely done by a wide variety of practitioners of medicine with a high degree of safety from spinal cord damage, since the spinal cord itself normally ends at the L1-L2 level in the adult human.

4C depicts an arrangement in which the main catheter 36 is inserted into one of the lateral ventricles, while the secondary catheter 37 is located in the C1-C2

subarachnoid space. This arrangement will promote better temperature modulation in the distal brainstem and cerebellum than is possible with a single lateral ventricle catheter since the CSF fluid in the brain is in continuity with that of the spinal cord. Good temperature modulation over both brain hemispheres is expected with only a single catheter, however.

Fig. 5 A proof-of-concept study was conducted on an adolescent pig (40 lbs) using certain elements of the disclosed invention for the purpose of a feasibility demonstration of brain cooling with intracranial pressure (ICP) control.

**Methods:** A manually operated CSF recirculation apparatus was assembled consisting of a refrigerated bath, two peristaltic pumps, and a double-barreled catheter. The animal was intubated and monitored under general anesthesia for: rectal body temperature (controlled at 37°C using a heating pad), arterial pressure, heart rate and ECG. The double-barreled catheter was inserted into the right lateral ventricle at an entry point 1 cm anterior to the coronal fissure and 1 cm lateral to the midline, while a standard external ventricular drain catheter (single lumen) was inserted into the left lateral ventricle and connected to a hygrometer for intracranial pressure (ICP) measurement. A temperature probe was inserted into the brain parenchyma to a depth of 1 cm in the left parietooccipital region for measurement of brain temperature on the side contralateral to the cooling catheter. The system was primed with 1 L artificial CSF (ACSF) of standard composition chilled to -2°C and continuously bubbled with 95%$O_2$/5%$CO_2$ (carbogen) gas. The two peristaltic pumps, one for CSF withdrawal (outflow) and one for CSF reintroduction (inflow), circulated the chilled CSF/ACSF to and from an open refrigerated container and were manually controlled. In essence, the flow rate was determined by the withdrawal pump and measured at intervals by collecting with withdrawn fluid in a graduated cylinder, while the introduction pump was constantly readjusted to maintain the desired ICP.

**Results:** The results of three runs at different flow rates are presented in Fig 1. As shown, higher flow rates and greater ICP's led to faster brain cooling in the presence of normal rectal temperatures. The ICP effect is presumably related to a decrease in cerebral blood flow and, consequently, of heat input to the brain. Therapeutic temperatures (<33°C) could be attained within 15 min without any perturbations in anaesthetic delivery, arterial pressure, heart rate, or EKG. Passive

rewarming between the second and third trials led to a rise in heart rate and arterial pressure when brain temperature reached 34°C, which was controlled by reactivating the cooling system at a low flow rate to slow the pace of rewarming. The animal was euthanized at the conclusion of the experiment and autopsied. No gross disruption of cerebral anatomy was evident, except for a 1 cm stab injury to the right thalamus caused by initially advancing the cooling catheter too far. This experiment demonstrates that rapid selective cooling of the entire brain with active ICP control is feasible using this form of CSF recirculation in the lateral ventricle.

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What is claimed is:

1. A method for precisely modulating the temperature and pressure within a body cavity for therapeutic purposes by means of recirculation of a biological or biocompatible fluid within the cavity, but outside of blood vessels, comprising the steps of:

infusing fluid by means of a pump at a controlled temperature and flow rate into the cavity;

monitoring the temperature and pressure within the cavity;

withdrawing fluid by means of a pump at a controlled flow rate from the cavity;

feedback adjustment of the outflow rate according to the measured intra-cavity temperature to achieve pre-programmed temperature targets over long time periods (hours to days) by means of a computer-automated controller system;

feedback adjustment of the inflow rate according to the measured intra-cavity pressure to achieve pre-programmed pressure targets (which may be adjusted based on the intracavity temperature) over long time periods (hours to days) by means of a computer-automated controller system.

2. The method of claim 1, wherein the infusion of fluid is through one barrel, and the withdrawal of fluid is through the other barrel of a double-barreled catheter inserted into the body cavity.

3. The method of claim 1, wherein a second, single barreled catheter may be inserted into an extremity of the cavity, and from which fluid is also pumped, but at a slower rate relative to the double-barreled catheter, in order to improve the distribution of recirculated fluid, and hence temperature control, throughout the cavity.

4. The method of claim 1, further comprising a temperature sensor capable of sensing the temperature of the fluid removed from the cavity by the second catheter.

5. The method of claim 1, further comprising a feedback regulation of the outflow rate of the second catheter based on the temperature of the fluid removed by this catheter.

6. The method of claim 1, wherein the recirculated fluid is extracorporeally heated or cooled by means of a feedback controlled heater/chiller to achieve a desired temperature.

7. The method of claim 1, wherein additional fluid is constantly added to the recirculated fluid in the system by gravity feed at a user-controlled rate.

8. The method of claim 1, further comprising a means of adding drugs or other agents to the recirculated fluid via the additional fluid pathway.

9. The method of claim 1, wherein a gas is bubbled through a reservoir containing the recirculating fluid in order to affect oxygenation, pH balancing or other chemical alteration of the fluid, as well as separation of contaminants by foam fractionation.

10. The method of claim 1, wherein the inflow rate is feedback adjusted according to intra-cavity temperature and the outflow rate is feedback adjusted according to intra-cavity pressure.

11. A method for the continuous removal of dissolved proteins or other contaminants by foam fractionation from a biological or biocompatible fluid intended for recirculation in a body cavity comprising the steps of:

collection of the fluid in an extracorporeal chamber;

continuous bubbling of the fluid with fine bubbles of air or other gas;

continuous overflow of the superficial layer of fluid and foam arising from the bubbles into a collecting reservoir.

12. The method of claim 11, wherein the continuous overflow method of skimming off superficial contaminants is replaced by suctioning off the superficial layer.

13. The method of claim 11, wherein the continuous overflow method of skimming off superficial contaminants is replaced by the collection of superficial foam in a collection cup as it rises in an enclosed space above the fluid.

14. The method of claim 11, wherein bubbling of the fluid is replaced by spraying the fluid with a jet of gas-fluid mixture.

15. The method of claim 11, wherein bubbling of the fluid is replaced by passing the fluid over a series of obstacles at high velocity within a chamber that also contains the gas.

16. The method of claim 11, wherein bubbling of the fluid is replaced by violent mixing of fluid and gas using a motorized impeller.

17. The method of claim 11, wherein bubbling of the fluid is replaced by introducing the gas using a Venturi tube into a rapidly flowing stream of fluid driven by a motor.

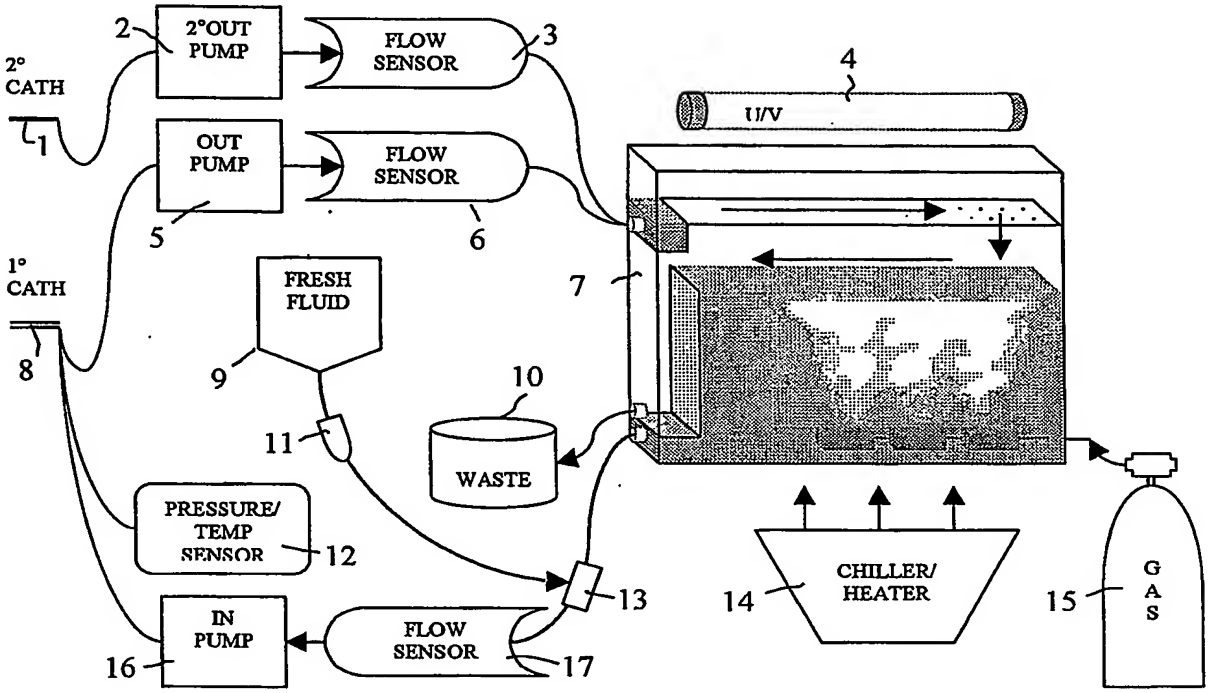
18. A double-barreled catheter design for recirculation of fluid within a body cavity consisting of:

two adjacent barrels of the same length in contact with one another along their length, one for infusion of the fluid into the body cavity (inflow) and one for outflow of the fluid;

distal ends of the barrels (the extremity of the catheter located inside the cavity) which are occluded by rounded caps;

one or more apertures in the sides of each of the barrels near the distal tip such that the flow from the outflow barrel aperture(s) is partially directed across the inflow aperture(s).

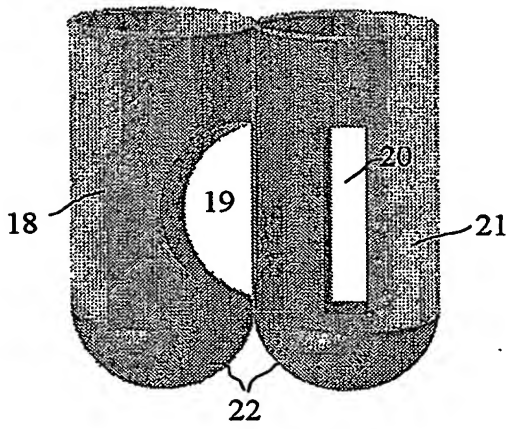
Fig. 1



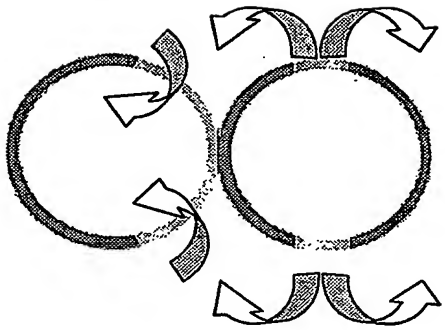

| COMPUTER-AUTOMATED CONTROLLER | | | |
|---|---|---|---|
| INPUTS: | Intra-cavity Temp<br>Intra-cavity Pressure<br>Conditioning Chamber Temp<br>Inflow Rate<br>Outflow Rate<br>2° Catheter Fluid Temp<br>Connection Status, Main Cath<br>Battery Status | OUTPUTS: | IN Pump RPMs<br>IN Pump direction<br>IN Pump on/off<br>OUT Pump RPMs<br>OUT Pump direction<br>OUT Pump on/off<br>Chill or Heat<br>Chiller/Heater power<br>2° OUT Pump RPMs<br>2° OUT Pump direction<br>2° OUT Pump on/off |

Fig. 2

A)




B)



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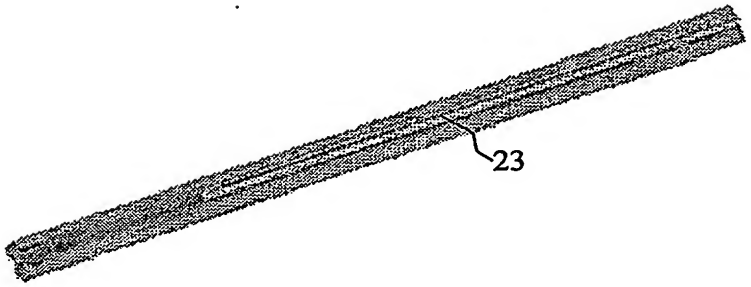


Fig. 3



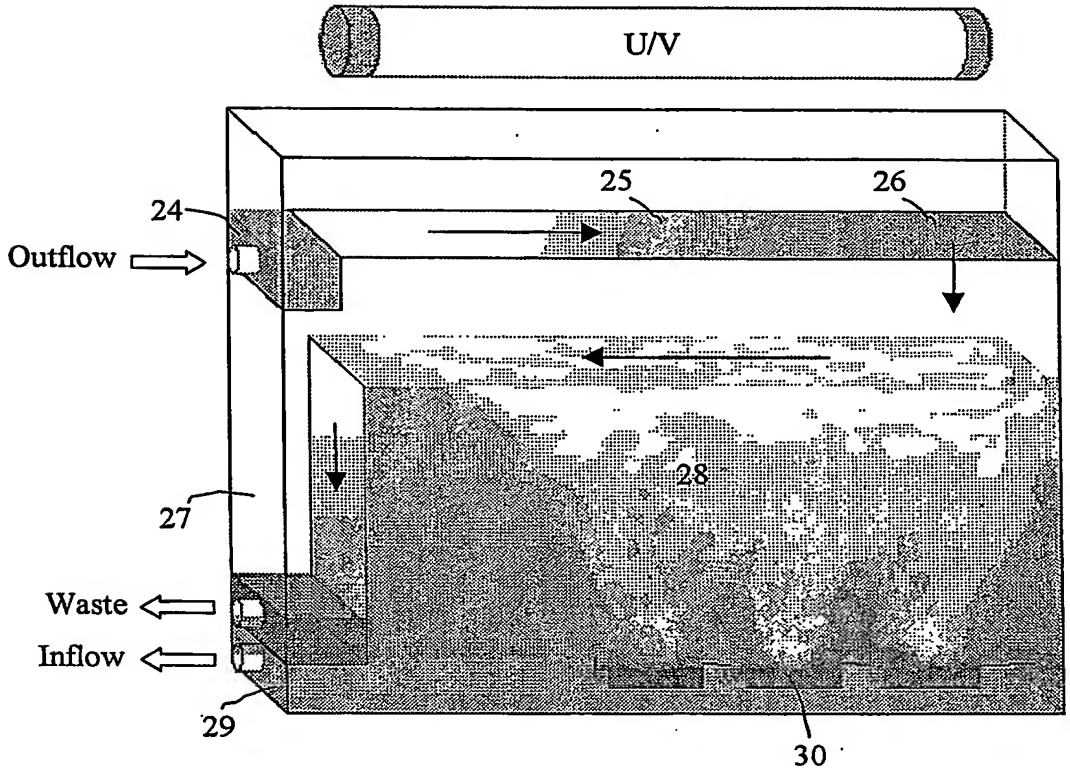
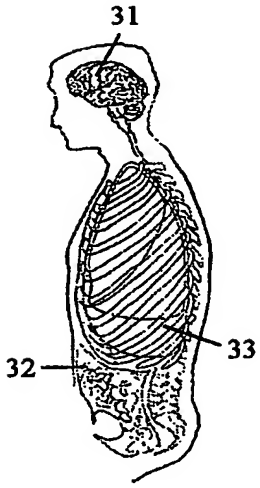
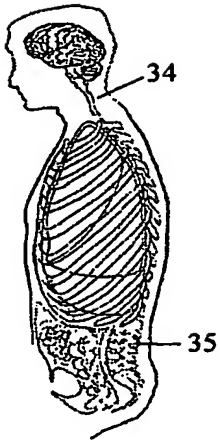


Fig 4




A)

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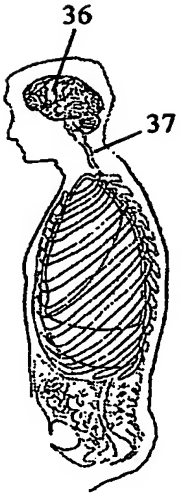


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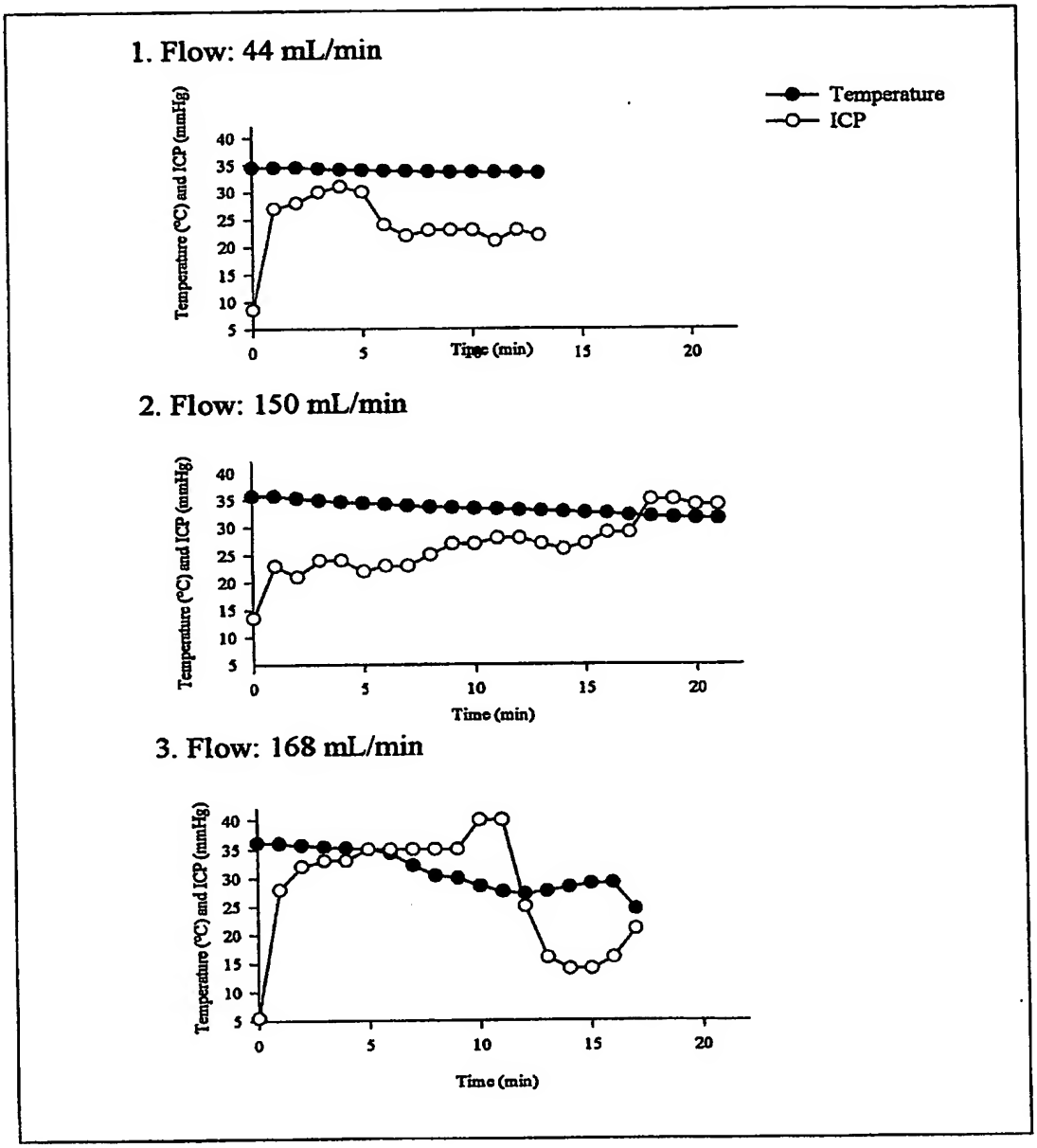


**Fig. 5** Selective brain cooling trials in a single pig under general anaesthesia (ICP = intracranial pressure). A brain temperature of 24°C was obtained within 20 min in trial 3. Note the facilitating effect of higher ICP in trial 3. The brain was allowed to rewarm fully between trials. Flow was determined by the outflow rate, while ICP was controlled by manual adjustment of the inflow rate. Body temperature was maintained at 37°C using a heating pad. Brain temperature was measured in the parietal parenchyma on the side contralateral to the cooling catheter.